

REMARKS

Upon entry of the amendment the pending claims will be 1 and 3-9.

No new matter is presented by the above amendments.

Applicants reserve the right to pursue unclaimed subject matter in continuing or divisional applications.

Rejections Under 35 USC 112

Claims 1-9 stand rejected under 35 USC 112, second paragraph as not being enabled for all vitamin D compounds. The Examiner has agreed that the claims are enabled with respect to the compounds disclosed at page 3, line 11 through page 4, line 5. While applicants disagree with the Examiner's conclusion, we note that claim 1 has been amended to recite vitamin D<sub>2</sub> and vitamin D<sub>3</sub> compounds and derivatives thereof.

Applicants reserve the right to pursue additional vitamin D compounds in continuing or divisional applications.

Claim 2 stands rejected under 35 USC 112, second paragraph as being indefinite.

Applicants have cancelled claim 2.

Rejections Under 35 USC 103

Claims 1-9 stand rejected under 35 USC 103 as unpatentable over Knutson et al (US Patent 5,869,473) and ZEMPLAR® monograph (Physician's Desk Reference, April 1998, page 478-480). The Examiner states that Knutson teaches 1,25-dihydroxy vitamin D3 is useful to increase serum calcium level and suppressing parathyroid hormone (PTH) level at a dosage of 0.5 µg. The ZEMPLAR monograph is cited as teaching that 1,25-dihydroxy-19-nor ergocalciferol is useful to increase serum calcium and suppressing PTH at a dosage of 2.8-7 µg. Applicants respectfully traverse the rejection.

To begin, Applicants would like to reiterate that the present invention is directed to a method for treating ICU-associated hypocalcemia. Hypocalcemia, as defined herein, is a reduction in the ionized calcium below the normal validated range (for a given hospital laboratory). Currently, hypocalcemia in an intensive care unit (ICU) setting is either not treated or it is treated only when the medical professional judges it to be of life threatening severity. Existing treatment modalities for hypocalcemia in this setting are limited to intravenous (IV) infusions of inorganic (e.g., CaCl<sub>2</sub>) or organic (e.g., calcium gluconate) salts. The problems associated with the administration of calcium salts are: (a) IV calcium infusions have attendant risk of cardiotoxicity, (b) IV calcium infusions only treat the manifestations of the abnormality, i.e., low ionized calcium, not the metabolic cause of the abnormality, (c) because ICU-related hypocalcemia reflects a blood/tissue maldistribution of calcium and not a net calcium loss the

administration of calcium may cause total calcium overload, and (d) calcium infusions are given as a "sliding scale" (increasing degrees of hypocalcemia relative to increasing doses of IV calcium) (see, specification, page 1). The inventors have discovered that compounds of the vitamin D class, including analogs and derivatives of vitamin D-type compounds, have utility in treating ICU-related hypocalcemia.

In the present case, it may be helpful to understand the differences between patients with End Stage Renal Disease (ESRD) and those with ICU-related hypocalcemia. Patients with ESRD have impaired kidney function and may have elevated blood levels of PTH. Thus, ESRD patients are treated with vitamin D-type compounds in an attempt to lower PTH. One of the secondary effects of lowering a patient's PTH is an increase in serum calcium.

In contrast, a patient with ICU-related hypocalcemia has decreased blood levels of calcium but will typically not have impaired kidney function. That is, an ICU patient may have a serum calcium level that is from 10-25% below normal but have PTH levels that are within the normal range. Thus, the use of 1,25-dihydroxy vitamin D<sub>3</sub> or ZEMPLAR® to lower PTH while raising serum calcium can not render obvious the use of vitamin D compounds to raise serum calcium while maintaining normal ranges of PTH. Therefore, reconsideration is respectfully requested.

### CONCLUSION

The prior art of record does not suggest the use of the present invention. A favorable action on Claims 1 and 3-9 is earnestly solicited.



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**VERSION WITH MARKINGS TO SHOW CHANGES**

1 A method for treating ICU-associated hypocalcemia in a mammal to restore or maintain ionized serum calcium in said mammal which comprises administering to said mammal a therapeutically effective amount of a [vitamin D compound] vitamin D<sub>2</sub>, vitamin D<sub>2</sub> derivative, vitamin D<sub>3</sub>, or vitamin D<sub>3</sub> derivative.